The attached paper copy and computer-readable copy of the Sequence Listing are submitted in compliance with 37 C.F.R. §§1.821-1.825. The contents of the paper copy and the computer-readable copy of the Sequence Listing are the same. No new matter is added. Support for the information provided in the Sequence Listing can be found in the original Sequence Listing.

Early and favorable consideration on the merits is respectfully requested.

Respectfully submitted,

William P. Berridge
Registration No. 30,024

Melanie L. Mealy
Registration No. 40,085

WPB:MLM/cmm

Attachment:
Appendix
Sequence Listing (paper and computer readable copies)

Date: September 18, 2001

OLIFF & BERRIDGE, PLC
P.O. Box 19928
Alexandria, Virginia 22320
Telephone: (703) 836-6400

DEPOSIT ACCOUNT USE AUTHORIZATION
Please grant any extension necessary for entry;
Charge any fee due to our Deposit Account No. 15-0461

APPENDIX

Changes to Specification:

The Sequence Listing is replaced

Page 10, line 1- page 11, line 29:

The set of Vβ molecules is termed the "Vβ repertoire" of the T lymphocytes. The various Vβ molecules are detected specifically, using at least one of the techniques described below:

(a) either using at least one ligand, i.e. any molecule capable of recognizing specifically the Vβ to be detected, for example an anti-Vβ monoclonal or polyclonal antibody, or a monoclonal or polyclonal antibody fragment, or a molecule which inhibits the function of the Vβ under consideration. The percentage of Vβ molecules of the repertoire is then related to the percentage of cells exhibiting the CD3 molecule at their surface, the latter also being detected specifically using at least one ligand. The term "ligand" is intended to mean in particular a monoclonal or polyclonal antibody, or a fragment of said antibodies, preferably a monoclonal antibody. The monoclonal antibodies directed against a Vβ of interest are produced by conventional techniques used to produce antibodies against surface antigens. Mice or rabbits are immunized (i) either with a natural or recombinant protein, (ii) with an immunogenic peptide, (iii) or with murine cells which express the protein or the peptide of interest and MHCII molecules. The Balb/c murine line is the most commonly used. The immunogen may also be a peptide chosen from the peptides defined from the primary sequences of the Vβs of interest. The proteins or peptides are coupled to keyhole limpet hemocyanin (peptide-KLH), as a support for ~~its~~ their use in immunization, or coupled to human serum albumin (peptide-HSA). The animals are given an injection of peptide-KLH or of peptide-HSA, using complete Freund's adjuvant (IFA). The sera and the hybridoma culture supernatants derived from the animals immunized with each peptide are analyzed for the presence of antibodies with an ELISA assay using the

initial molecules. The spleen cells of these mice are recovered and fused with myeloma cells. Polyethylene glycol (PEG) is the most commonly used fusion agent. The hybridomas producing the most specific and the most sensitive antibodies are selected. The monoclonal antibodies can be produced *in vitro* by cell culture of the hybridomas produced or by recovering murine ascites fluid after intraperitoneal injection of the hybridomas into mice. Whatever the method of production as supernatant or as ascites, it is then important to purify the monoclonal antibody. The purification methods used are essentially filtration over ion exchange gel or by exclusion chromatography, or even immunoprecipitation. For each antibody, the method which will make it possible to obtain the best yield should be chosen. A sufficient number of antibodies is screened in functional assays in order to identify the antibodies which are the most effective in binding the molecule of interest and/or in blocking the activity of the molecule of interest. The selected monoclonal antibodies are humanized using standard "CDR grafting" methods (protocol carried out by many companies, in the form of a service). These humanized antibodies can be tested clinically in patients. The effectiveness of these antibodies can be monitored using clinical parameters. The *in vitro* production of antibodies, of antibody fragments or of antibody derivatives, such as chimeric antibodies which may or may not be humanized and which are produced by genetic engineering, in eukaryotic cells has been described (EP 120 694 or EP 125 023) and can also be applied to the present invention;

Page 19, line 35- page 20, line 29:

In order to evaluate the effectiveness of the molecules for therapeutic use, i.e. one or more molecule(s) capable of inhibiting the expansion or the loss of the T lymphocytes of a given Vβ, ~~a culture supernatant of blood mononucleated cells, of choroid plexus cells or of leptomeningeal cells is sampled, said cells originating from patients suffering from an autoimmune disease, in particular from MS,~~

(i) blood mononucleated cells are sampled, said cells originating from patients suffering from an autoimmune disease or suspected or having a risk of developing the disease, in particular MS, and from healthy individuals,

(ii) said blood mononucleated cells originating from MS patients or from healthy individuals are brought into contact with culture supernatants, or a fraction of culture supernatant, of cells chosen from blood mononucleated cells, choroid plexus cells, leptomeningeal cells and cells derived from established cell lines, such as the cells of the PLI-2 cell line and the LM7PC cell line, and

(iii) the inhibition of said expansion and, optionally, co-expansion, or the inhibition of said loss and, optionally, co-decrease, of the lymphocytes bearing at least one determinant chosen from Vβ16, Vβ2, Vβ3, Vβ7, Vβ8, Vβ12, Vβ14, Vβ17 and Vβ22, in particular Vβ16 and/or Vβ17, Vβ16, Vβ3 and Vβ12 or Vβ16, Vβ7, Vβ14 and Vβ17, particularly Vβ16, Vβ7 and Vβ17, using the blood mononucleated cells of step (i), in the presence of said ~~agent or of said composition~~molecule at given doses, are detected using a ligand as described above or amplification combined with electrophoresis as described above.

Page 29, lines 28-34:

On the basis of the amino acid sequence of the molecules of interest of the invention, peptide sequences of these molecules or fragments of peptides sequences of these molecules, corresponding to all or part of the primary sequence of these molecules, ~~and~~ can be synthesized using conventional methods of peptide synthesis or obtained by genetic recombination.

Page 33, line 3- page 34, line 35:

The *in vitro* production of antibodies, of antibody fragments or of antibody derivatives, such as chimeric antibodies which may or may not be humanized and which are produced by genetic engineering, in eukaryotic cells has been described (EP 120 694 or EP 125 023) and can also be applied to the present invention,

- at least one molecule which inhibits the function of at least one molecule chosen from the molecules of interest of the invention or the fragments thereof,

- at least one molecule which regulates the expression of at least one molecule chosen from the molecules of interest of the invention or the fragments thereof, for example to block the transcription or the translation of these molecules,

- at least one molecule which regulates the metabolism of at least one protein chosen from the molecules of interest of the invention or the fragments thereof,

- at least one molecule which regulates the expression and/or the metabolism of a ligand for at least one protein chosen from the molecules of interest of the invention or the fragments thereof, for example a receptor or a cofactor,

- at least one nucleic acid sequence comprising at least one gene of therapeutic interest, the nucleic acid sequence of which is deduced from the DNA and RNA sequences encoding all or part of the molecules of interest of the invention, in combination with elements which ensure the expression of said gene of therapeutic interest *in vivo* in target cells intended to be genetically modified with the nucleic acid sequence of the gene of therapeutic interest. The genes may or may not be mutated. They may also consist of nucleic acids modified such that it is not possible for them to integrate into the genome of the target cell, or of nucleic acids stabilized using agents such as spermine. Such a gene of therapeutic interest in particular encodes-:

- at least ~~encodes~~ a protein chosen from the molecules of interest identified in the present invention or the fragments thereof, and/or

- at least ~~encodes~~ a ligand or any part of a ligand capable of attaching to at least one protein or one protein fragment chosen from the molecules of interest identified in the present invention or the fragments thereof, which may or may not inhibit the function of the molecule of interest, and/or

- at least ~~encodes~~ all or part of a polyclonal or monoclonal antibody capable of attaching to at least one protein or one protein fragment chosen from the molecules of interest identified in the present invention or the fragments thereof, which may or may not inhibit the function of the molecule of interest. It may in particular be a native transmembrane antibody, or a fragment or derivative of such an antibody, provided that said antibody, antibody fragment or antibody derivative is expressed at the surface of the genetically modified mammalian target cell and is capable of binding to a polypeptide present at the surface of a cytotoxic effector cell or of a helper T lymphocyte involved in the process of activation of such a cell, and/or

- at least ~~encodes~~ a molecule which inhibits at least one protein or the fragments thereof, said protein being chosen from the molecules of interest identified in the present invention, which can inhibit the function and/or the metabolism and/or the binding of the molecules of interest or of the fragments thereof.

Page 35, line 26- page 36, line 16:

The nucleic acid sequence is preferably a DNA or RNA sequence which is naked, i.e. free of any compound which facilitates its introduction into cells (nucleic acid sequence transfer). However, according to a second embodiment of the invention, in order to promote its introduction into target cells and in order to obtain the genetically modified cells of the invention, this nucleic acid sequence may be in the form of a "vector", and more particularly in the form of a viral vector, such as for example an adenoviral vector, a retroviral vector or a vector derived from a poxvirus, in particular derived from the vaccinia virus or from the Modified Virus Ankara (MVA), or of a nonviral vector, such as for example a vector consisting of at least one said nucleic acid sequence complexed with or conjugated to at least one carrier molecule or substance selected from the group consisting of a cationic amphiphile, in particular a cationic lipid, a cationic or neutral polymer, a polar ~~practical~~ proctic compound, in particular chosen from propylene glycol, polyethylene glycol, glycerol, ethanol, 1-methyl-L-2-pyrrolidone,

or derivatives thereof, and a polar aprotic compound, in particular chosen from dimethyl sulfoxide (DMSO), diethyl sulfoxide, di-n-propyl sulfoxide, dimethylsulfone, sulfolane, dimethylformamide, dimethylacetamide, tetramethylurea, acetonitrile, or derivatives thereof. The literature provides a considerable number of examples of such viral and nonviral vectors.

Page 39, line 1- page 40, line 6:

These nucleic acid sequences and/or vectors make it possible to target the cells in which the protein or the protein fragment is expressed, either using a targeting molecule introduced onto the vector or using a particular property of the cell;

- at least one mammalian cell which does not naturally produce at least one molecule of interest of the invention or any fragment of these molecules, or antibodies specific for at least one of said molecules of interest of the invention or of the fragments thereof, said mammalian cell being genetically modified *in vitro* with at least one nucleic acid sequence or a fragment of a nucleic acid sequence or a combination of nucleic acid sequences corresponding to nucleic acid fragments derived from the same gene or from different genes, said nucleic acid sequence(s) being deduced from the DNA and RNA sequences encoding the molecules of interest of the invention or any fragment, said gene of therapeutic interest encoding all or part of the molecule of interest of the invention, of a fragment of the molecule or of an antibody specific for the molecule which will be expressed at the surface of said mammalian cell (Toes et al., 1997, PNAS 94: 14660-14665). Thus, said cell contains at least one gene which encodes *in vivo*:

- at least one protein chosen from the molecules of interest of the invention and/or the fragments thereof, and/or

- at least one peptide defined on the basis of the primary sequence of at least one protein chosen from the molecules of interest of the invention and/or the fragments thereof, and/or

- at least any molecule which inhibits the activity and/or the binding and/or the expression of these molecules, and/or

- at least one peptide derived from the primary sequence of a protein chosen from the molecules of interest of the invention and/or the fragments thereof, and capable of binding to at least one MHCI and/or MHCII glycoprotein, and/or

- at least one ligand and/or any antibody and/or any part of an antibody capable of binding to at least one protein chosen from the molecules of interest of the invention and/or the fragments.

Page 40, lines 17-30:

The invention also relates to the modified cells and a method for preparing a cell as described above, characterized in that at least one nucleic acid sequence containing at least one gene of therapeutic interest and elements which ensure the expression of said gene in said cell are introduced into a mammalian cell by any ~~or~~ suitable means, said gene of therapeutic interest containing a nucleic acid sequence encoding a molecule or a molecule fragment *in vivo*, as described just above. More particularly, it relates to prokaryotic cells, yeast cells and animal cells, in particular mammalian cells, transformed with at least one nucleotide sequence and/or one vector as described above.

Page 45, lines 2-35:

In particular, the therapeutic and/or prophylactic agent is chosen from DNA and/or RNA molecules; antisense oligonucleotides and anti-gene oligonucleotides; at least one ligand capable of interacting with Vβ16 and/or Vβ17, in particular Vβ16, optionally in combination with at least one ligand capable of interacting with at least one of Vβ2, Vβ3, Vβ7, Vβ8, Vβ12, Vβ14, Vβ17 and Vβ22, and preferentially Vβ3 and Vβ12; from antibodies, preferably monoclonal antibodies and anti-receptors for the TCRs of the various Vβs above; at least one ligand capable of interacting with Vβ16 and/or Vβ17, optionally in combination with at least one ligand capable

of interacting with at least one of Vβ7, Vβ14, Vβ17 and Vβ22, and preferentially Vβ7 and Vβ17, in particular antibodies, and preferably monoclonal antibodies, or fragments of said antibodies and anti-receptors for the TCRs of the various Vβs above; an agent capable of blocking the interaction of the superantigen with the antigen-presenting cells; at least one cell, preferably a cell of mammalian origin, genetically modified *in vitro* with a therapeutic agent which consists of at least one nucleic acid molecule encoding at least one molecule, the protein sequence of which corresponds to the sequence encoding the molecules as defined above, in particular a DNA and/or RNA molecule; at least one cell, preferably a cell of mammalian origin, genetically modified *in vitro* with a therapeutic agent which consists of at least one nucleic acid molecule encoding at least one ligand as defined above, in particular a DNA and/or RNA molecule~~; and the uses thereof for prophylaxis and/or the treatment of a pathological condition, in particular an autoimmune disease such as multiple sclerosis~~.

Page 46, lines 7-28:

In particular, the therapeutic and/or prophylactic agent is chosen from DNA and/or RNA molecules; antisense oligonucleotides and anti-gene oligonucleotides; at least one ligand capable of interacting with MSRV-1 proteins, in particular the env protein of MSRV-1, from antibodies, preferably monoclonal antibodies and anti-MSRV-1 proteins, in particular anti-env proteins of MSRV-1; at least one cell, preferably a cell of mammalian origin, genetically modified in vitro with a therapeutic agent which consists of at least one DNA molecule encoding at least one molecule, the protein sequence of which corresponds to the sequence encoding the molecules as defined above, in particular a DNA and/or RNA molecule; at least one cell, preferably a cell of mammalian origin, genetically modified in vitro with a therapeutic agent which consists of at least one DNA molecule encoding at least one ligand as defined above, in particular a DNA and/or RNA molecule~~; and the uses for the prophylaxis and/or the treatment of a pathological condition, in particular an autoimmune disease such as multiple sclerosis~~.

Page 51, line 10- page 52, line 17:

The invention relates to the *in vivo* expression of nucleotide sequences and/or of vectors as described above, i.e. sequences corresponding to genes of therapeutic interest, in particular:

- either at least encoding a protein chosen from the molecules of interest identified in the present invention or the fragments thereof; and/or

- ~~or~~ at least encoding all or part of a polyclonal or monoclonal antibody capable of binding to at least one protein chosen from the molecules of interest identified in the present invention and the fragments thereof. It may be a native transmembrane antibody, or a fragment or derivative of such an antibody, provided that said antibody, antibody fragment or antibody derivative is expressed at the surface of the genetically modified mammalian target cell and that said antibody is capable of binding to a polypeptide present at the surface of a cytotoxic effector cell or of a helper T lymphocyte and inhibiting the activity of at least one molecule of interest of the invention. They may be antibody fragments expressed by cells capable of secreting said antibodies into the blood circulation of a mammal or patient carrying the cells genetically modified with the gene encoding the antibody; and/or

- ~~or~~ at least encoding a molecule which inhibits at least one protein chosen from the molecules identified in the present invention or the fragments thereof; and/or

- ~~or~~ at least encoding a ligand or any part of the ligand capable of binding to at least one protein chosen from the molecules of interest identified in the present invention or the fragments thereof, and/or of inhibiting its function. Using the amino acid sequences of the molecules of interest of the invention or of the fragments thereof, it is within the scope of those skilled in the art to deduce the DNA and RNA nucleotide sequences corresponding to the molecules of interest or to the fragments thereof, using the genetic code and taking into account the degeneracy thereof. Thus, the present invention relates to the use of these nucleotide sequences in the form of antisense sequences, of sequences encoding a therapeutic gene and of

sequences which can be contained in a vector for performing cell transformation *ex vitro* and/or *in vivo* (gene therapy).

Page 55, lines 13-38:

According to a particular embodiment, cytotoxic effector cells or helper T lymphocytes are genetically modified, in particular *in vivo*, so that they express, at their surface, ligands for at least one of said molecules of interest of the invention, which are not naturally expressed by these cells, and which are capable of binding to all or part of at least one of the molecules of interest of the invention at the surface of the same cell or of another cell, and of inhibiting the activity of at least one molecule of interest of the invention, by introducing into these cells nucleic acid sequences containing the gene encoding such a polypeptide. In accordance with the present invention, it is also possible to select a nucleic acid sequence containing a gene of therapeutic interest encoding all or part of an antibody directed against a protein chosen from the molecules of interest of the invention and the peptide sequences and/or the fragments of said sequences, which is capable of being expressed at the surface of the target cells of the patient to be treated, said antibody being capable of binding, via these effector cells, to a polypeptide of the molecules of interest of the invention present at the surface of the cytotoxic lymphocytes and/or helper T lymphocytes, or even of inhibiting the activity of these molecules of interest.

Page 63, lines 21-37:

Human lymphocytes are isolated from 50 ml of heparinized blood diluted 50/50 with RPMI 1640, by centrifugation on a Ficoll gradient. They are carefully harvested from the band, as are possible cellular aggregates which may float just above the band. The cells are then washed twice in RPMI 1640 medium. After these washes, the cells are resuspended at the concentration of $2 \times$ ~~106~~ 10^6 cells/ml in RPMI 1640 medium containing:

200 U/ml penicillin

20 mg/l streptomycin

6 mM L-glutamine

1% sodium pyruvate

1% essential amino acids

anti-leukocytic IFN antibody (polyclonal anti-alpha interferon sold by Sigma) added to 10 U/ml final.

Page 72, lines 3-8:

Two mixtures of antibodies were used to detect the presence of viral antigens in the human lymphocytes cultured in the presence of extracts of LES and GRE choroid plexus CS, under the same conditions as for the analysis of the expansion of the TCR (T-cell receptor) Vβ families ~~was carried out~~.

Page 78, lines 4-12:

Example 12: Stimulation of cytokine production.

The cultures of lymphocytes stimulated with MSBL differ in that they produce significantly greater amounts of IL-6 and of γ-INF compared to those stimulated with CTBL. On the other hand, the TNF-α titers are very low and equivalent for the two types of culture. The results, expressed in pg/ml of culture corresponding to 2×10^6 cells, ~~. These results~~ are shown in Table 5.

Page 78, lines 17-28:

Example 13: Detection of viral antigens in the lymphocyte cultures.

The presence of specific retroviral antigens was investigated using the two pools of antibodies directed against MSRV-1 proteins. The results of immunofluorescence on the cultures inoculated with LES or GRE ultracentrifuged CS, obtained with the two pools (pool 2 = mouse monoclonals, pool 1 = rabbit polyclonals), are shown in Table 46 for donors 10 and 11. The numbers represent the percentages of cells exhibiting fluorescence intensities included between channels 100 and 1000.

Changes to Claims:

Claims 72 and 75-77 are canceled.

Claims 4-14, 18-25, 28, 31, 33-47, 50-57, 60-68, 70, 71, 73 and 74 are amended.

The following are marked-up versions of the amended claims:

4. (Amended) The method as claimed in claim 2, characterized in that a majority expansion of lymphocytes bearing a Vβ16 determinant and a co-expansion of lymphocytes bearing Vβs chosen from at least any one of Vβ2, Vβ3, Vβ7, Vβ8, Vβ12, Vβ14, Vβ17 and Vβ22~~, and preferably of Vβ3 and Vβ12,~~ are demonstrated.

5. (Amended) The method as claimed in claim 3, characterized in that a majority loss of lymphocytes bearing a Vβ16 determinant and ~~of [sic]~~ a co-decrease of lymphocytes bearing Vβs chosen from at least any one of Vβ2, Vβ3, Vβ7, Vβ8, Vβ12, Vβ14, Vβ17 and Vβ22~~, preferably at least any one of Vβ7, Vβ14 and Vβ17, and advantageously of Vβ7 and Vβ17,~~ are demonstrated.

6. (Amended) The method as claimed in ~~any one of the preceding claims~~ claim 1, characterized in that the biological sample originates from a patient suffering from an autoimmune disease~~, in particular multiple sclerosis~~.

7. (Amended) The method for detecting superantigen activity as claimed in ~~any one of claims 1 to 6~~ claim 1, characterized in that:

(i) a culture supernatant of blood mononucleated cells or of choroid plexus cells or of leptomeningeal cells, said cells originating from patients suffering from an autoimmune disease or suspected of having a risk of developing the disease~~, in particular multiple sclerosis,~~ or of an established cell line~~, such as the cells of the PLI-2 cell line deposited at the ECACC on July 22, 1992, under the number 92072201 and the LM7PC cell line deposited at the ECACC on January 8, 1993, under the number 93010817, in accordance with the provisions of the Treaty of Budapest,~~ is sampled, and

(ii) said culture supernatant, or a part of the culture supernatant is brought into contact with a series of cultures~~, preferably at least three,~~ of blood mononucleated cells originating from healthy donors, and

(iii) said expansion and, optionally, a co-expansion, or said loss and, optionally, co-decrease, of the blood mononucleated cells of step (ii) are detected.

8. (Amended) The method as claimed in claim 7, characterized in that the blood mononucleated cells originating from patients originate from patients suffering from multiple sclerosis (MS) and are chosen from monocytes and B lymphocytes and the blood mononucleated cells originating from healthy donors are chosen from T lymphocytes.

9. (Amended) The method for detecting superantigen activity as claimed in ~~any one of claims 1 to 6~~ claim 1, characterized in that:

(i) blood mononucleated cells are sampled, said cells originating from patients suffering from an autoimmune disease or from patients suspected of having a risk of developing an autoimmune disease, ~~in particular MS,~~ and from healthy individuals,

(ii) said blood mononucleated cells originating from patients or from healthy individuals are brought into contact with culture supernatants, or a fraction of culture supernatant, of cells chosen from blood mononucleated cells, choroid plexus cells and leptomeningeal cells, and cells derived from established cell lines, ~~such as the cells of the PLI-2 cell line deposited at the ECACC on July 22, 1992, under the number 92072201 and the LM7PC cell line deposited at the ECACC on January 8, 1993, under the number 93010817, in accordance with the provisions of the Treaty of Budapest,~~ and

(iii) said expansion and, optionally, co-expansion, or said loss and, optionally, co-decrease, using the blood mononucleated cells of step (i) are detected.

10. (Amended) The method as claimed in ~~claims 7, 8 and 9~~ claim 7, characterized in that said expansion and, optionally, co-expansion is demonstrated using ligands, each ligand

being specific for a determinant chosen from Vβ16, Vβ2, Vβ3, Vβ7, Vβ8, Vβ12, Vβ14, Vβ17 and Vβ22, ~~preferably Vβ16, Vβ3 and Vβ12,~~ and in that said loss and, optionally co-decrease is demonstrated using ligands, each ligand being specific for a determinant chosen from Vβ16, Vβ2, Vβ3, Vβ7, Vβ8, Vβ12, Vβ14, Vβ17 and Vβ22~~, preferably Vβ16, Vβ7, Vβ14 and Vβ17~~.

11. (Amended) The method as claimed in claim 10, characterized in that the ligand is an antibody~~, preferably a monoclonal antibody or an antibody fragment~~.

12. (Amended) The method as claimed in claim 7~~, 8 and 9~~, characterized in that in order to demonstrate said expansion and, optionally, co-expansion or said loss and, optionally, co-decrease, the following is carried out

(i) extraction of the total RNAs from the blood mononucleated cells which have been placed together with MS culture supernatant or a fraction of MS culture supernatant and together with control culture supernatant or a fraction of control culture supernatant,

(ii) reverse transcription of said RNAs,

(iii) amplification specific for each Vβ family using a given pair of primers,

(iv) labeling of the amplification products obtained, with any suitable label,

(v) electrophoresis of said amplification products and analysis of the electrophoretic profiles obtained, using a suitable detector.

13. (Amended) The method as claimed in claim 12, characterized in that the blood mononucleated cells originating from patients originate from patients suffering from MS and are chosen from lymphocytes.

14. (Amended) A method for detecting a pathological condition or a predisposition to a pathological condition, in a biological sample, characterized in that at least one of the following parameters is demonstrated:

superantigen activity, ~~as defined in any one of claims 1 to 13,~~ characterized in that a majority expansion of lymphocytes bearing a Vβ16 and/or Vβ17 determinant or a majority loss of lymphocytes bearing a Vβ16 and/or Vβ17 determinant is demonstrated,

stimulation of the production of cytokines, ~~such as interleukin-6 (IL-6) and γ-interferon (γ-INF),~~ and

induction of cellular apoptosis.

18. (Amended) The method as claimed in claim 7, ~~8 and 9~~, characterized in that the pathological condition is associated with an autoimmune disease, ~~such as multiple sclerosis~~.

19. (Amended) The method as claimed in ~~any one of the preceding claims~~ claim 1, characterized in that the superantigen activity is induced directly or indirectly by an effector agent chosen from proteins and/or microorganisms and/or pathogenic agents.

20. (Amended) The method as claimed in claim 19, characterized in that the microorganism is chosen from bacteria and retroviruses, ~~preferably human retroviruses, and in particular the retrovirus is MSRV-1 (Multiple sclerosis retrovirus 1) and in particular the pathogenic agent is MSRV-2 (Multiple sclerosis retrovirus 2)~~.

21. (Amended) The method as claimed in ~~claims 19 and 20~~ claim 19, characterized in that the superantigen activity is induced by the envelope protein of MSRV-1 referenced in SEQ ID No. 2 or by a fragment of said protein.

22. (Amended) The method as claimed in ~~claims 19 and 20~~ claim 19, characterized in that the superantigen activity is induced by the *env* gene of MSRV-1 referenced in SEQ ID No. 1 or a fragment of said gene.

23. (Amended) A human retrovirus, ~~in particular an endogenous retrovirus,~~ which has superantigen activity and is associated with an autoimmune disease, characterized in that the retrovirus is MSRV-1 and in that the superantigen activity is induced by the expression of the

env gene of MSRV-1 or of a fragment of said gene~~, in particular a fragment of said gene encoding at least one reading frame of the env protein of MSRV-1 (SEQ ID No. 2)~~.

24. (Amended) A human retrovirus,~~ in particular an endogenous retrovirus,~~ which has superantigen activity and is associated with an autoimmune disease, characterized in that the retrovirus is MSRV-1 and in that the superantigen activity is induced by the env protein of MSRV-1 or by a fragment of said protein~~, in particular by a fragment corresponding to at least one reading frame of said protein (SEQ ID No. 2)~~.

25. (Amended) A nucleic acid molecule comprising at least one or more fragment(s) of the RNA or of the DNA of the *env* gene of MSRV-1, identified by SEQ ID No. 1, said fragment being at least 18 nucleotides~~, and preferably at least 24 nucleotides,~~ in length.

28. (Amended) A polypeptide molecule~~, in particular protein or protein fragment~~ comprising at least one or more fragment(s) of ~~said~~ the env protein of MSRV-1 identified by SEQ ID No. 2, said fragment being at least 6 amino acids~~, and preferably at least 8 amino acids,~~ in length.

31. (Amended) A vector comprising nucleic acid molecules as defined in ~~claims 25 to 27~~ claim 25.

33. (Amended) The method as claimed in claim 32, characterized in that:

(i) a culture supernatant of blood mononucleated cells or of choroid plexus cells or of leptomeningeal cells, said cells originating from patients suffering from an autoimmune disease or suspected of having a risk of developing the disease~~, in particular multiple sclerosis,~~ or of an established cell line,~~ such as the cells of the PLI-2 cell line deposited at the ECACC on July 22, 1992, under the number 92072201 and the LM7PC cell line deposited at the ECACC on January 8, 1993, under the number 93010817, in accordance with the provisions of the Treaty of Budapest,~~ is sampled, and

(ii) said culture supernatant, or a part of the culture supernatant is brought into contact with a series of cultures~~, preferably at least three,~~ of blood mononucleated cells originating from healthy donors, and

(iii) said expansion and, optionally, a co-expansion, or said loss and, optionally, co-decrease, of the blood mononucleated cells of step (ii) are detected.

34. (Amended) The method as claimed in claim 33, characterized in that the blood mononucleated cells originating from patients originate from patients suffering from MS and are chosen from B lymphocytes and monocytes and the blood mononucleated cells originating from healthy donors are chosen from T lymphocytes.

35. (Amended) The method as claimed in claim 32, characterized in that:

(i) blood mononucleated cells are sampled, said cells originating from patients suffering from an autoimmune disease or from patients suspected of having a risk of developing an autoimmune disease~~, in particular MS,~~ and from healthy individuals,

(ii) said blood mononucleated cells originating from patients or from healthy individuals are brought into contact with culture supernatants, or a fraction of culture supernatant, of cells chosen from blood mononucleated cells, choroid plexus cells and leptomeningeal cells, and cells derived from established cell lines~~, such as the cells of the PLI-2 cell line deposited at the ECACC on July 22, 1992, under the number 92072201 and the LM7PC cell line deposited at the ECACC on January 8, 1993, under the number 93010817, in accordance with the provisions of the Treaty of Budapest,~~ and

(iii) said expansion and, optionally, co-expansion, or said loss and, optionally, co-decrease, using the blood mononucleated cells of step (i) are detected.

36. (Amended) The method as claimed in claim 32, characterized in that:

(i) a culture supernatant of blood mononucleated cells or of choroid plexus cells or of leptomeningeal cells, said cells originating from patients suffering from an autoimmune

disease or suspected of having a risk of developing the disease or of an established cell line, is sampled, and

(ii) said culture supernatant, or a part of the culture supernatant is brought into contact with a series of cultures of blood mononucleated cells originating from healthy donors, and

(iii) said expansion and, optionally, a co-expansion, or said loss and, optionally, co-decrease, of the blood mononucleated cells of step (ii) are detected ~~the superantigen activity is demonstrated according to a protocol as described in claims 10 to 12,~~ using a ligand or amplification combined with electrophoresis.

37. (Amended) The method for detecting superantigen activity as claimed in ~~any one of claims 1 to 6~~ claim 1, characterized in that

(i) a polypeptide~~, in particular a recombinant protein,~~ as identified by SEQ ID No. 2, or a fragment of said polypeptide ~~or of said protein~~, is produced or synthesized,

(ii) said polypeptide ~~or said protein~~ is brought into contact with a series of cultures~~, preferably at least three,~~ of blood mononucleated cells originating from healthy donors, and

(iii) said expansion and, optionally, a co-expansion, or said loss and, optionally, co-decrease, of the blood mononucleated cells of step (ii) are detected.

38. (Amended) The method for detecting superantigen activity as claimed in ~~any one of claims 1 to 6~~ claim 1, characterized in that:

(i) blood mononucleated cells are sampled, said cells originating from patients suffering from an autoimmune disease or from patients suspected of having a risk of developing an autoimmune disease~~, in particular MS,~~ and from healthy individuals,

(ii) said blood mononucleated cells originating from patients or from healthy individuals are brought into contact with a polypeptide or a recombinant protein, as identified in SEQ ID No. 2, or a fragment of said polypeptide ~~or of said protein~~, and

(iii) said expansion and, optionally, co-expansion, or said loss and, optionally, co-decrease, using the blood mononucleated cells of step (i) are detected.

39. (Amended) The method as claimed in claim 38, characterized in that a polypeptide ~~as defined in claims 28 to 30~~ comprising at least one or more fragment(s) of the env protein of MSRV-1 identified by SEQ ID No. 2, said fragment being at least 6 amino acids in length, is used.

40. (Amended) The method as claimed in claim 37 ~~or 38~~, characterized in that said polypeptide is encoded by a nucleic acid ~~as defined in claims 26 to 27~~ comprising at least one or more fragment(s) of the RNA or of the DNA of the *env* gene of MSRV-1, identified by SEQ ID No. 1, said fragment being at least 18 nucleotides in length, or a vector ~~as claimed in claim 31~~ comprising said nucleic acid.

41. (Amended) A method for evaluating the effectiveness of an agent or of a composition in inhibiting superantigen activity in a biological sample, characterized in that

(i) a culture supernatant of blood mononucleated cells, or of choroid plexus cells or of leptomeningeal cells, said cells originating from patients suffering from an autoimmune disease~~, in particular MS,~~ or of cells of an established cell line, ~~such as the cells of the PLI-2 line and the LM7PC line,~~ is sampled,

(ii) said supernatant, or a part of the culture supernatant, is brought into contact with a series of cultures~~, preferably at least three,~~ of blood mononucleated cells originating from healthy donors, in the presence of said agent or of said composition at predetermined doses, and

(iii) the inhibition of said expansion and, optionally, co-expansion, or the inhibition of said loss and, optionally, co-decrease, of the lymphocytes bearing at least one

determinant chosen from Vβ16, Vβ2, Vβ3, Vβ7, Vβ8, Vβ12, Vβ14, Vβ17 and Vβ22~~, in particular Vβ16 and/or Vβ17, Vβ16, Vβ3 and Vβ12 or Vβ16, Vβ7, Vβ14 and Vβ17, particularly Vβ16, Vβ7 and Vβ17,~~ are detected using a ligand ~~as described in claims 10 and 11~~ specific for said determinant or amplification specific for each Vβ family using a given pair of primers combined with electrophoresis ~~as described in claim 12~~ of said amplification products.

42. (Amended) A method for evaluating the effectiveness of an agent or of a composition in inhibiting superantigen activity in a biological sample, characterized in that

(i) a polypeptide~~, in particular a recombinant protein~~ is produced or synthesized,

(ii) said polypeptide ~~or recombinant protein~~ is brought into contact with a series of cultures~~, preferably at least three,~~ of blood mononucleated cells originating from healthy donors, in the presence of said agent or of said composition at predetermined doses, and

(iii) the inhibition of said expansion and, optionally, co-expansion, or the inhibition of said loss and, optionally, co-decrease, of the lymphocytes bearing at least one determinant chosen from Vβ16, Vβ2, Vβ3, Vβ7, Vβ8, Vβ12, Vβ14, Vβ17 and Vβ22~~, in particular Vβ16 and/or Vβ17, Vβ16, Vβ3 and Vβ12 or Vβ16, Vβ7, Vβ14 and Vβ17, particularly Vβ16, Vβ7 and Vβ17,~~ are detected using a ligand ~~as described in claims 10 and 11~~ specific for said determinant or amplification specific for each Vβ family using a given pair of primers combined with electrophoresis ~~as described in claim 12~~ of said amplification products.

43. (Amended) A method for evaluating the effectiveness of an agent or of a composition in inhibiting superantigen activity in a biological sample, characterized in that

(i) blood mononucleated cells are sampled, said cells originating from patients suffering from an autoimmune disease or suspected of having a risk of developing the disease, ~~in particular MS,~~ and from healthy individuals,

(ii) said blood mononucleated cells originating from patients or from healthy individuals are brought into contact with culture supernatants, or a fraction of culture

supernatant, of cells chosen from blood mononucleated cells, choroid plexus cells, leptomeningeal cells and cells derived from established cell lines, ~~such as the cells of the PLI-2 cell line and the LM7PC cell line,~~ and

(iii) the inhibition of said expansion and, optionally, co-expansion, or the inhibition of said loss and, optionally, co-decrease, of the lymphocytes bearing at least one determinant chosen from Vβ16, Vβ2, Vβ3, Vβ7, Vβ8, Vβ12, Vβ14, Vβ17 and Vβ22~~, in particular Vβ16 and/or Vβ17, Vβ16, Vβ3 and Vβ12 or Vβ16, Vβ7, Vβ14 and Vβ17, particularly Vβ16, Vβ7 and Vβ17,~~ using the blood mononucleated cells of step (i), in the presence of said agent or of said composition at given doses, are detected using a ligand ~~as described in claims 10 and 11~~ specific for said determinant or amplification specific for each Vβ family using a given pair of primers combined with electrophoresis ~~as described in claim 12~~ of said amplification products.

44. (Amended) A method for evaluating the effectiveness of an agent or of a composition in inhibiting superantigen activity in a biological sample, characterized in that

(i) blood mononucleated cells are sampled, said cells originating from patients suffering from an autoimmune disease or suspected of having a risk of developing the disease~~, in particular MS,~~ and from healthy individuals,

(ii) said blood mononucleated cells originating from patients or from healthy individuals are brought into contact with a polypeptide or a recombinant protein, and

(iii) the inhibition of said expansion and, optionally, co-expansion, or the inhibition of said loss and, optionally, co-decrease, of the lymphocytes bearing at least one determinant chosen from Vβ16, Vβ2, Vβ3, Vβ7, Vβ8, Vβ12, Vβ14, Vβ17 and Vβ22~~, in particular Vβ16 and/or Vβ17, Vβ16, Vβ3 and Vβ12 or Vβ16, Vβ7, Vβ14 and Vβ17, particularly Vβ16, Vβ7 and Vβ17,~~ using the blood mononucleated cells of step (i), in the presence of said agent or of said composition at given doses, are detected using a ligand ~~as~~

~~described in claims 10 and 11~~ specific for said determinant or amplification specific for each Vβ family using a given pair of primers combined with electrophoresis ~~as described in claim 12~~ of said amplification products.

45. (Amended) The method as claimed in ~~any one of claims 41 to 44~~ claim 41, characterized in that the cells originate from a patient suffering from an autoimmune disease~~, in particular multiple sclerosis~~.

46. (Amended) The method as claimed in ~~any one of claims 41 to 45~~ claim 41, characterized in that the blood mononucleated cells ~~originating~~ originate from patients suffering from MS and are chosen from B lymphocytes and monocytes.

47. (Amended) A method for evaluating the prophylactic and/or therapeutic effectiveness of an agent or of a composition with respect to a pathological condition and/or to a predisposition to a pathological condition, characterized in that inhibition of superantigen activity in a biological sample is demonstrated as described in ~~claims 41 to 46~~ claim 41.

50. (Amended) The method as claimed in ~~either of claims 48 and 49~~ claim 48, characterized in that the cells originate from a patient suffering from an autoimmune disease~~, such as multiple sclerosis~~.

51. (Amended) The method as claimed in ~~claims 48 to 50~~ claim 48, characterized in that the blood mononucleated cells ~~originating~~ originate from patients suffering from MS and are chosen from B lymphocytes and monocytes.

52. (Amended) A method for evaluating the prophylactic and/or therapeutic effectiveness of an agent or of a composition with respect to a pathological condition and/or to a predisposition to a pathological condition, characterized in that inhibition of superantigen activity in a biological sample is demonstrated as described in ~~claims 48 to 51~~ claim 48.

53. (Amended) Composition for therapeutic and/or prophylactic use, characterized in that it comprises, inter alia, a therapeutic agent capable of inhibiting superantigen activity in a

biological sample, ~~as defined in claims 1 to 6,~~ said superantigen activity being characterized in that a majority expansion of lymphocytes bearing a Vβ16 and/or Vβ17 determinant or a majority loss of lymphocytes bearing a Vβ16 and/or Vβ17 determinant is demonstrated, optionally in combination with a pharmaceutically acceptable excipient and/or adjuvant and/or diluent.

54. (Amended) The composition as claimed in claim 53, characterized in that the therapeutic agent is an antiviral agent~~, more particularly an antiretroviral agent, in particular a human antiretroviral agent, preferably an anti-MSRV1 agent, such as an inhibitor of the replication cycle and/or of the expression of a retrovirus, such as an anti-retroviral protein antibody, in particular an anti-envelope antibody, such as antisense oligonucleotides, more particularly which block retroviral expression~~.

55. (Amended) Composition as claimed in claim 53, characterized in that the therapeutic agent is chosen from a natural molecule and/or a recombinant molecule, or a fragment of said molecules, the protein sequence of which corresponds to the sequence of the Vβ16 and/or Vβ17 molecules, ~~preferably the Vβ16 molecule,~~ optionally in combination with one or more natural and/or recombinant molecules, or a fragment of said molecules, the protein sequence of which corresponds to the sequence of the Vβ2, Vβ3, Vβ7, Vβ8, Vβ12, Vβ14, Vβ17 and Vβ22 molecules~~, and preferentially of the Vβ3 and Vβ12 molecules~~.

56. (Amended) Composition as claimed in claim 53, characterized in that the therapeutic agent is chosen from a natural molecule and/or a recombinant molecule, or a fragment of said molecules, the protein sequence of which corresponds to the sequence of the Vβ16 and/or Vβ17 molecules, and optionally in combination with one or more natural and/or recombinant molecules or a fragment of said ~~modules~~ molecules, the protein sequence of which corresponds to the Vβ7, Vβ14 and Vβ17 molecules~~, and preferentially of the Vβ7 and Vβ17 molecules~~.

57. (Amended) The composition as claimed in claim 53, characterized in that the therapeutic agent is chosen from the natural and/or recombinant and/or synthetic molecules, or a fragment of said molecules~~, which encode the molecules as defined in claims 53 to 56~~.

60. (Amended) The prophylactic and/or therapeutic composition as claimed in claim 53, characterized in that the prophylactic and/or therapeutic agent is chosen from at least one ligand capable of interacting with Vβ16 and/or Vβ17, ~~in particular Vβ16,~~ optionally in combination with at least one ligand capable of interacting with at least one of Vβ2, Vβ3, Vβ7, Vβ8, Vβ12, Vβ14, Vβ17 and Vβ22~~, and preferentially Vβ3 and Vβ12~~.

61. (Amended) The composition as claimed in claim 60, characterized in that the ligand is capable of interacting with a retrovirus, ~~in particular a human retrovirus, such as MSRV-1,~~ its proteins and/or its nucleic acids.

62. (Amended) The composition as claimed in claim 60, characterized in that the ligand is an antiviral agent~~, more particularly an antiviral agent, in particular a human antiviral agent, preferably an anti-MSRV1 agent, such as an inhibitor of the replication cycle and/or of the expression of a retrovirus, such as an anti-retroviral protein antibody, in particular an anti-envelope antibody, such as antisense oligonucleotides, more particularly which block retroviral expression~~.

63. (Amended) The composition as claimed in claim 60, characterized in that the ligand is chosen from antibodies~~, preferably monoclonal antibodies and anti-receptors for the T-cell receptors (TCRs) of the various Vβs~~.

64. (Amended) The composition as claimed in claim 61, characterized in that the ligand is chosen from anti-MSRV-1 antibodies~~, preferably monoclonal antibodies~~.

65. (Amended) The prophylactic and/or therapeutic composition as claimed in claim 53, characterized in that the prophylactic and/or therapeutic agent is chosen from at least one ligand capable of interacting with Vβ16 and/or Vβ17, optionally in combination with at

least one ligand capable of interacting with at least one of Vβ7, Vβ14, ~~v~~Vβ17 and Vβ22~~, and preferentially Vβ7 and Vβ17~~.

66. (Amended) ~~[sic]~~ The composition as claimed in claim 60, characterized in that the ligand is capable of interacting with a retrovirus, ~~in particular a human retrovirus, such as MSRV-1,~~ its proteins and/or its nucleic acids.

67. (Amended) The composition as claimed in claim 63~~ or 65~~, characterized in that the ligand is chosen from antibodies~~, preferably monoclonal antibodies and anti-receptors for the TCRs of the various Vβs~~.

68. (Amended) The composition as claimed in claim 63~~ or 64~~, characterized in that the ligand is chosen from anti-MSRV-1 antibodies~~, preferably monoclonal antibodies~~.

70. (Amended) A therapeutic and/or prophylactic composition, characterized in that the therapeutic and/or prophylactic agent is chosen from at least one cell~~, preferably a cell of mammalian origin,~~ genetically modified *in vitro* with a therapeutic agent which consists of at least one nucleic acid molecule encoding at least one molecule, the protein sequence of which ~~corresponds to the sequence encoding the molecules as defined in claims 1 to 5, 10, 20 to 31 and 53 to 59, in particular a DNA and/or RNA molecule~~ has a superantigen activity characterized in that a majority expansion of lymphocytes bearing a Vβ16 and/or Vβ17 determinant or a majority loss of lymphocytes bearing a Vβ16 and/or Vβ17 determinant is demonstrated.

71. (Amended) The composition as claimed in claim 53, characterized in that the therapeutic and/or prophylactic agent is chosen from at least one cell~~, preferably a cell of mammalian origin,~~ genetically modified *in vitro* with a therapeutic agent which consists of at least one nucleic acid molecule encoding at least one ligand ~~as defined in claims 60 to 69, in particular a DNA and/or RNA molecule~~ capable of interacting with Vβ16 and/or Vβ17.

73. (Amended) A method for identifying substances capable of blocking the transcription and/or the translation of a human retrovirus, ~~in particular a retrovirus which is~~

~~endogenous, as defined in claims 23 and 24, and which has superantigen activity, said superantigen activity being associated with an autoimmune disease,~~ according to which,

the substance is brought into contact with cells expressing a retroviral polypeptide ~~as defined in claims 28 to 30~~, which has superantigen activity, said polypeptide comprising at least one or more fragment(s) of the env protein of MSRV-1 identified by SEQ ID No. 2, said fragment being at least 6 amino acids in length, and

a loss or decrease of the superantigen activity is detected as described in ~~claims 1 to 6~~ claim 1.

74. (Amended) A kit for screening substances capable of blocking the superantigen activity of a retrovirus~~, in particular an endogenous human retrovirus,~~ associated with an autoimmune disease, or capable of blocking the transcription and/or the translation of said retrovirus, comprising:

cells expressing, at their surface, class II MHC products, transformed with and functionally expressing a retroviral superantigen,

cells bearing receptor chains having one or more Vβs stimulated by the retroviral superantigen, and

means for detecting a loss or decrease of the superantigen activity as described in ~~claims 1 to 6~~ claim 1.